I. DEFINITION AND ETIOLOGY

Definition: chronic kidney disease (CKD) represents the slow, progressive and irreversible decrease of the glomerular filtration rate (GFR) < 60 ml/min/1.73 m², over a minimum 3-month period.

Etiology: CKD is the terminal stage of chronic progressive nephropathies which include:

1. Glomerular nephropathies:
   - severe glomerulonephritis (80% of CKD cases)
   - diabetic nephropathy
   - renal amyloidosis
2. Renal vascular nephropathies:
   - malignant hypertension
   - hypertension nephroangiosclerosis
   - bilateral renal artery sclerosis
3. Tubulointerstitial nephropathies
   - chronic pyelonephritis
4. Obstructive uropathy
5. Renal cystic disease

Important!
Diabetes mellitus and arterial hypertension are responsible for most CKD cases. With the increase in life expectancy and the ageing of the world population, with the accelerated prevalence of diabetic and cardiovascular diseases, CKD represents a public health problem, currently underdiagnosed and detected at a relatively late stage of its progression.

II. PATHOGENESIS

CKD is characterised by 2 major pathogenic processes:

A. IRREVERSIBLE and PROGRESSIVE damage of FUNCTIONAL NEPHRONS

Characteristics:

1. The progression of diabetic nephropathy to CKD implies a decrease in the number of functional nephrons due to their destruction by initial pathological processes:
   - Initial glomerular or vascular impairment induces proteinuria, haematuria
tubulointerstitial damage initially involves renal tubules or the renal medulla inducing natrium loss, the alteration of the dilution capacity and urine concentration, renal tubular acidosis

2. Regardless the initial impairment, CKD also involves the progressive loss of functional nephrons through a common pathogenic mechanism which includes:
   - Intraglomerular hypertension, hypertrophy and adaptive hyperfiltration of the surviving nephrons
   - Inflammation of the mesangium and glomerulosclerosis
   - Inflammation of the renal interstitium and tubulointerstitial fibrosis

3. Decreased GFR with excretory function disorders is progressively associated with disorders of the regulatory and endocrine functions of the kidney

4. The severity of the natural progression of the damage (defined by the annual decrease of the GFR) greatly differs from case to case (from a few months up to several years), as shown below, in descending order:

   Ischaemic nephropathy > diabetic nephropathy > glomerular (non-diabetic) nephropathies > tubulointerstitial nephropathies > hypertensive nephropathy > renal cystic disease

B. COMPENSATORY alterations in the SURVIVING NEPHRONS ("the intact nephron hypothesis")

1. MORPHOLOGICAL and FUNCTIONAL hypertrophy

   PATHOGENIC mechanism:
   - Is mediated by cytokines and growth factors in order to mobilise the functional reserve defined by increased glomerular filtration (adaptive hyperfiltration), increased reabsorption and tubular secretion → mobilisation of the functional reserve makes possible the conservation of renal excretory function up to the point when the ratio of surviving nephrons decreases < 25% (obvious exhaustion of adaptive functional reserve)
   - Is more obvious in young people, less obvious in older ones, and extremely obvious in patients with only one kidney (post nephrectomy)

   Consequences: adaptive hyperfiltration in surviving nephrons ensures maintaining GFR within normal limits over a longer period of time, however with „price” of intraglomerular hypertension responsible for:

   ① The development of systemic hypertension
   ② Triggering the common pathogenic mechanism of CKD progression → proteinuria and increased angiotensin II production (AII) which represent the key factors:
      - adaptive hyperfiltration induces protein filtration through the glomerular membrane which initially:
        ✓ accumulate in the mesangial area and trigger inflammation and glomerulosclerosis
        ✓ are reabsorbed in the tubules and trigger inflammation and tubulointerstitial fibrosis
      - adaptive hyperfiltration involves increased AII production — responsible for:
        ✓ intraglomerular hypertension and development of systemic arterial HT by arteriolar vasoconstriction
        ✓ promoting inflammation by stimulating local inflammatory cell activity (mainly macrophages)
        ✓ promoting tubulointerstitial fibrosis by: chronic tubulointerstitial ischaemia (vasoconstriction of the afferent arteriole) and release of growth factors

2. COMPENSATORY polyuria

   The decrease of GFR is compensated through osmotic diuresis which induces an increase of natrium and water excretion fraction by decreasing tubular reabsorption.

   a) Increase of NATRIUM and WATER EXCRETION FRACTION
      ① In normal subjects: releasing an osmotic charge of 600 mOsm/day, with a GFR = 125 ml/min which induces the formation of 180 litres of primary urine/day, can be achieved by a volume of 2 litres of final urine with an osmolality of 300 mOsm/L corresponding to a natrium and water excretion fraction of 1% of the primary urine
In CKD patients: in order to eliminate the same osmotic charge of 600 mOsm/day, with a GFR = 125 ml/min which induces the formation of only 40 litres of primary urine/day, to obtain 2 litres of final urine with an osmolality of 300 mOsm/L requires a natrium and water excretion fraction of 5% of the primary urine → a fraction 5 times greater than normal has to be eliminated from the overall filtrated volume, which can only be achieved by decreasing tubular natrium and water reabsorption

b) OSMOTIC diuresis and DECREASED TUBULAR REABSORPTION

In normal subjects: the osmotic charge of 600 mOsmol/day is excreted by 100% of the nephrons

In CKD patients: the osmotic charge of 600 mOsmol/day can be excreted by less than 20% of the nephrons → the osmotic charge/surviving nephron increases 5 times and has 2 consequences:
- tubular osmotic surcharge retains water and induces osmotic diuresis → decreased water tubular reabsorption
- osmotic diuresis increases primary urine flow in the surviving nephron and decreases the contact time between the tubular fluid and the reabsorption surface → decreased natrium and water tubular reabsorption

III. CKD DISORDERS

A. EXCRETORY FUNCTION disorder. ACCUMULATION OF UREMIC TOXINS

- Cause: decreased GFR → defines the severity of renal function impairment (Tab.1)

Table 1. Stages of CKD according to GFR decrease and the SEVERITY OF RENAL FUNCTION IMPAIRMENT

<table>
<thead>
<tr>
<th>Stage</th>
<th>GFR (ml/min/1.73 m²)</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>&gt; 90</td>
<td>Chronic kidney damage with normal GFR</td>
</tr>
<tr>
<td>II</td>
<td>60 – 89</td>
<td>Chronic kidney damage with slightly lower GFR</td>
</tr>
<tr>
<td>IIIa</td>
<td>45 – 59</td>
<td>CKD with slightly to moderately decreased GFR</td>
</tr>
<tr>
<td>IIIb</td>
<td>30 – 44</td>
<td>CKD with moderately to severely decreased GFR</td>
</tr>
<tr>
<td>IV</td>
<td>15 – 29</td>
<td>CKD with severely decreased GFR</td>
</tr>
<tr>
<td>V</td>
<td>&lt; 15</td>
<td>Renal failure</td>
</tr>
</tbody>
</table>


- Consequences:
  1. Adaptive hyperfiltration in surviving nephrons which represent < 50% of the total number ensures the elimination of the same quantity of substances resulting from cell catabolism (e. g., uremic toxins) or from the exogenous input (e. g., Na⁺ and water) like a normal kidney:
    - osmotic surcharge per nephron → osmotic diuresis
    - capacitation of the anatomical and functional reserve → impaired capacity of the kidney to adapt to the overload caused by the alterations of cell catabolism or exogenous input
  2. Decreased number of surviving nephrons < 10% of the normal number induces:
    - impaired elimination of substances resulting from cell catabolism or from the exogenous input → uremic syndrome (chronic uraemia)
    - exhaustion of the anatomical and functional reserve → renal failure

Important!
The normal elimination of a substance by renal pathway is ensured by the proportional increase of its plasma concentration. For example, an increased creatinine plasma concentration represents a
compensatory mechanism for a decreased GFR which forces renal elimination of urine, according to the formula:

\[ Q_{Cr} = GFR \times PCr \]

Where:
- \( Q_{Cr} \) = quantity of creatinine eliminated by the kidneys
- \( GFR \) = glomerular filtration rate
- \( PCr \) = plasma creatinine concentration

The formula above shows that once GFR decreases to 50% of its normal value, the elimination of the same quantity of creatinine as in normal conditions requires the doubling of plasma creatinine concentration.

Accumulation of UREMIC TOXINS

- **Definitions**:
  - nitrogen retention (azotemia) = elevation of plasma urea, serum creatinine and uric acid induced by an impaired renal excretion function
  - uremic syndrome (chronic uraemia) = clinical biological syndrome induced by:
    1. plasma elevation of uremic toxins by the alteration of excretory function
    2. alteration of the regulatory function
    3. alteration of the kidney’s endocrine function

- **Uremic toxins** – comprise:
  - urea
  - guanidinic compounds (guanidine, methyl and dimethylguanidine, guanidinosuccinic acid, creatine and creatinine)
  - uric acid
  - aliphatic amines
  - aromatic amino acids
  - medium molecular weight polypeptides

- **Sources**:
  - accumulation of proteolytic catabolism products
  - alteration of hydroelectrolytic balance
  - metabolic acidosis
  - intestinal absorption of toxins produced by intestinal bacteria

**B. REGULATORY FUNCTION disorders**

1. **WATER BALANCE disorders**

- **Characteristics**:
  1. Water balance is steady but labile (the kidney CANNOT adapt to the overcharge imposed by the alterations of the extracellular volume)
  - exaggerated exogenous input → hyperhydration
  - excessive loss (e. g., vomiting, too many diuretics) → severe dehydration with hypovolemia and renal circulation disorders leading to acute tubular damage associated with existing CKD
  2. In CKD patients, there is a compensatory polyuria:
    - fixed → independent of the water intake
    - with isosthenuria → urinary density = 1.008–1.012, identical with that of primary urine (deproteinised plasma) due to impaired urine concentration and dilution capacity

**Important!**

Compensatory polyuria is a component of a progressive sequence in CKD which reflects the percentage of surviving nephrons as follows:
1. **Moderate polyuria with hyposthenuria** → < 50% of surviving nephrons
2. **Severe polyuria with fixed isosthenuria** → < 35% of surviving nephrons
3. **Pseudonormaluria (normal diuresis) with fixed isosthenuria** → < 25% of surviving nephrons
4. **Oligoanuria with fixed isosthenuria** → < 10% of surviving nephrons

- **The PATHOGENIC mechanism of ISOSTHENEURIA**: impairment of surviving nephrons by uremic toxins induces a diminished urine concentration and dilution capacity
  - osmotic diuresis and medullary interstitial damage annul the osmotic gradient in the renal medulla (corticopapillary osmotic gradient) → **alteration of the countercurrent multiplier mechanism which ensures urine concentration and dilution**
  - distal and collecting tubule damage → lack of response to ADH action (**ADH-insensitive polyuria**)

- **Consequences:**
  1. **In normal subjects:**
     - the kidney can adapt to very great variations in the water and mineral salt intake because its concentration and dilution capacities are **NORMAL**:
       - osmolality of final urine **may vary** between 50 and 1200 mOsm/l
       - density of final urine **may vary** between 1,005 and 1,040
       - diuresis **may vary** between 15 litres (maximum dilution in diabetes insipidus) and 0.5 litres (maximum concentration in severe dehydration)
  2. **In CKD patients:**
     - the kidney **CANNOT** adapt to very great variations in the water and mineral salt intake because its concentration and dilution capacities are **LOW**:
       - osmolality of final urine **is relatively constant** = 250-300 mOsm/l (close to that of final urine or of deproteinised plasma = **isosmolality**)
       - density of final urine **is relatively constant** = 1,008-1,012 (close to that of final urine or of deproteinised plasma = **isosthenuria**)
       - urinary volume **is relatively constant**: initially **polyuria** and then **oligoanuria**

2. **NATRIUM BALANCE disorders**

- **Characteristics**: Na\(^+\) balance is maintained within normal limits until the advanced stages due to the renally excreted Na\(^+\) fraction increase (obligatory loss of 20-40 mEq/day which has to be compensated by an increase of the exogenous input in order to prevent volemic decrease)

- **PATHOGENIC mechanisms**:
  1. **OSMOTIC diuresis**: elevation of primary urine flow in the surviving nephrons induces ↓ contact time of the tubular fluid with the reabsorption surface → decreased Na\(^+\) and water tubular reabsorption
  2. **Alteration of Starling forces in the PERITUBULAR CAPILLARIES** decrease Na\(^+\) and water tubular reabsorption in the proximal tubule
     - arterial hypertension associated with CKD induces increased hydrostatic pressure in the peritubular capillaries
     - hypalbuminemia due to impaired hepatic synthesis induces a drop of the oncotic pressure in the peritubular capillaries
     - presence of proteins in the primary urine induces an elevation of the tubular oncotic pressure
  3. **HIPPURATE retention and secretion** (anions eliminated renally through tubular secretion) induces decreased Na\(^+\) and water tubular reabsorption:
     - the transporters responsible for the secretion of hippuric acid **interfere with those used in Na\(^+\) reabsorption**
     - the hippuric acid has an osmotic effect and retains water
  4. **PROSTAGLANDIN release redirect** renal blood flow towards the cortical area where nephrons have a short Henle’s loop → impaired Na\(^+\) reabsorption in the ascending branch of Henle’s loop
  5. **Increased synthesis and release of the atrial natriuretic peptide** induces decreased Na\(^+\) reabsorption in the collecting tubule
**Partial inhibitor effect of UREMIC TOXINS on Na⁺/K⁺-dependent ATPase** induces ↓ of Na⁺ transportation from the tubular lumen to the renal interstitium and the peritubular capillaries, respectively

3. **POTASSIUM BALANCE disorders**

- **Characteristics:** K⁺ balance is maintained within normal limits until the advanced stages because K⁺ glomerular filtration decrease is compensated by:
  - decreased reabsorption in the PCT
  - increased secretion in the DT
  1. *normal:* glomerular filtered K⁺ is entirely reabsorbed in the proximal tubule, thus K⁺ present in the primary urine comes exclusively from the distal tubular secretion
  2. *in CKD:* the filtrated quantity decreases, the reabsorbed quantity decreases, and the distally secreted quantity increases (it may exceed the glomerularly filtrated quantity)
  - increased extrarenal elimination

- **PATHOGENIC mechanisms:**
  1. Decreased proximal reabsorption — is caused by osmotic diuresis and is associated with decreased Na⁺ reabsorption (*normal*, K⁺ is reabsorbed paracellularly based on the electric gradient achieved by Cl⁻ and Na⁺ reabsorption)
  2. Increased K⁺ secretion in the distal tubules — is caused by:
     - increased electronegativity of the tubular lumen by decreased anion absorption
     - increased tubular flow by osmotic diuresis
     - increased secretion stimulated by secondary hyperaldosteronism
  3. Increased extrarenal K⁺ elimination — is achieved by aldosterone-stimulated secretion in the colon
     (this compensatory mechanism is also involved in the elimination of non-protein nitrogen compounds, mainly in that of high concentrations of urea)

4. **PHOSPHOCALCIC BALANCE disorders**

- **PATHOGENIC mechanism:**
  - impaired GFR induces decreased phosphate elimination → hyperphosphatemia
  - hyperphosphatemia → hypocalcemia by increasing the P/Ca ratio, which leads to Ca²⁺ precipitation in tissues (mainly in bones)
  - hypocalcemia is aggravated by low Ca²⁺ intestinal absorption by hypovitaminosis D secondary to 1 α-hydroxylase inhibition (alteration of renal hydroxylation of 25-hydroxycholecalciferol)
  - hypocalcemia stimulates PTH secretion → secondary hyperPTH which:
    1. mobilises bone Ca²⁺ → bone demineralisation leading to the development of fibrocystic osteitis
    2. impaired renal phosphate reabsorption → ↓ phosphate elimination brings back to normal the P/Ca ratio

**Important!**
The persistence of secondary hyperPTH induces, in the advanced stages of CKD, a tertiary hyperPTH through parathyroid gland hyperplasia and is responsible for hypercalcemia + calcification of soft tissues (mainly vessels and heart) → increased cardiovascular risk

5. **ACID BASE BALANCE disorders**

- **Characteristics:** metabolic acidosis when GFR drops to 30-40% of its normal value

- **PATHOGENIC mechanisms:**
  1. Decreased GFR induces ↓ elimination of phosphate (HPO₄²⁻) and sulphate (SO₄²⁻) anions → their accumulation in the plasma consumes HCO₃⁻ in its attempt to buffer them
  2. Alteration of HCO₃⁻ repair renal mechanisms →
     - the first affected are renal ammoniagenesis and the HCO₃⁻ tubular reabsorption mechanism
– H+ secretion is maintained until GFR < 5% of the normal values
- Consumption of the bone buffer system → bone demineralisation (renal osteodystrophy or osteopathy)
- Respiratory compensation by hyperventilation → Cheynes-Stokes or Kussmaul dyspnoea

C. HORMONAL FUNCTION disorders

1. ERYTHROPOIETIN secretion disorder
   - Consequences: NORMOCHROMIC NORMOCYTIC anaemia
   - PATHOGENIC mechanisms:
     - pathological haemolysis – shortening of erythrocyte life span induced by uremic toxins
     - direct medullary inhibition – induced by uremic toxins
     - blood loss due to ulcerations of the digestive tract – common complication of chronic uraemia
     - relative erythropoietin deficit:
       ✓ erythropoietin concentration is NOT below normal, but it is lower compared to the degree of anaemia
       ✓ the kidney is NOT capable to increase erythropoietin secretion to values that would effectively stimulate haematogenous marrow

2. ACTIVE VITAMIN D secretion disorders (1.25- dihydroxycholecalciferol)
   - Causes: inhibition of 1 α₂-hydroxylase prevents the hydroxylation of 25-hydroxicalciferol (calcidiol) and the formation of 1.25- dihydroxycholecalciferol (calcitriol) which is the active form of vitamin D
   - Consequences:
     - decreased Ca²⁺ intestinal absorption → hypocalcemia
     - bone demineralisation → osteomalacia

3. RENIN secretion disorders
   - Characteristics:
     - renin synthesis alteration may occur in both directions → increased or decreased synthesis
     - in CKD the kidney loses the capacity of adapting renin secretion to the haemodynamic necessities
   - Increased renin synthesis:
     - is induced by renal ischaemia
     - leads to renovascular arterial HT (high renin level induces arterial HT)
   - Decreased renin synthesis:
     - may be caused by the destruction of renin secretory cells
     - appears in parenchymatous renal arterial HT (arterial HT inhibits renin secretion)

IV. MANIFESTATIONS OF CKD

A. Stages of CKD

CLINICAL- BIOLOGICAL SIGNS

CKD has 5 stages of development defined by the decrease of GFR and characterised by a clinical-biological picture which represents the renal functional reserve = the kidney's capacity to compensate for the functional overcharge induced by the increased cell catabolism or by the exogenous intake (Table.2).

Table 2. CLINICAL-BIOLOGICAL signs in CKD according to the SEVERITY OF RENAL IMPAIRMENT.

<table>
<thead>
<tr>
<th>Stage</th>
<th>GFR (ml/min/1.73 m²)</th>
<th>CLINICAL-BIOLOGICAL signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>&gt; 90</td>
<td>asymptomatic CKD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>only basic symptoms are visible</td>
</tr>
</tbody>
</table>
### B. URAEMIC syndrome (chronic uraemia)

- **Definition**: clinical-biological syndrome caused by the severe impairment of the excretory function of uremic toxins (GFR < 25% of its normal value), of the regulation and endocrine functions with metabolic and cellular renal disorders, and damage of all body systems and apparatuses (Table.3).

#### 1. METABOLIC disorders

- **Impaired glucose tolerance** and **hyperglycaemia** due to low deposits, increased mobilisation from the deposits and impaired glucose uptake – caused by:
  - **intracellular K⁺ deficit** resulting from partial blocking of Na⁺/K⁺-dependent ATPase and to the transmineralisation process (glucogen synthesis requires a normal intracellular K⁺ concentration)
  - **metabolic acidosis** which inhibits the intake and uptake of peripheral glucose by decreasing insulin resistance → **insulin resistance** (insulinaemia is normal or even slightly elevated)
  - **hyperglucagonaemia** caused by decreased glucagon catabolism (which normally takes place in the kidney) → high mobilisation of sugar from the deposits and hyperglycaemia

- **Dyslipidemia**:
  - increased VLDL and triglycerides due to increased hepatic synthesis as well as to decreased lipoprotein lipase activity which is eliminated renally through glomerular proteinuria
  - decreased HDL-C induced by the decreased lipoprotein lipase activity (decreased formation of native HDL particles which need cholesterol and phospholipid transfer from the VLDL particles and chylomicrons while these are subjected to the action of lipoprotein lipase) → **accelerated ATS**
• **Negative nitrogen balance** – due to:
  – impaired exogenous intake following **amino acid malabsorption** (malabsorption is explained by the digestive disorders in chronic uraemia)
  – increased cell metabolism → loss of muscle mass

2. **CELLULAR disorders**

- **Cause:** Na⁺/K⁺–dependent ATPase inhibition by uremic toxins
- **Consequences:**
  – transmineralisation – altered Na⁺ și K⁺ distribution in the intracellular and extracellular space
  – hypothermia – average internal t°C is 1°C lower than in healthy individuals

Table 3. Signs of the UREMIC SYNDROME and the corresponding PATHOGENIC mechanism.

<table>
<thead>
<tr>
<th>System</th>
<th>Signs</th>
<th>PATHOGENIC mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Central NS</td>
<td>Uremic encephalopathy</td>
<td>Neuron segmentation subsequent to elevated plasma osmolality (the osmotic gradient between extracellular and intracellular fluid)</td>
</tr>
<tr>
<td></td>
<td>- disorientation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- lethargy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- coma</td>
<td></td>
</tr>
<tr>
<td>2. Peripheral NS</td>
<td>Uremic polyneuritis</td>
<td>Interference of nervous transmission by uremic toxins</td>
</tr>
<tr>
<td></td>
<td>- Motor neuropathy (muscle weakness)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Sensitive neuropathy (parestesias)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Persistent hicough</td>
<td></td>
</tr>
<tr>
<td>3. Cardiovascular</td>
<td>Haemorrhagiparous syndrome</td>
<td>Decreased platelet function and coagulation factor synthesis</td>
</tr>
<tr>
<td></td>
<td>- Anaemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Uremic cardiomyopathy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Myocardial ischaemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Uremic pericarditis</td>
<td></td>
</tr>
<tr>
<td>4. Immune</td>
<td>Infections</td>
<td>Defective immune response</td>
</tr>
<tr>
<td>5. Digestive</td>
<td>Anorexia, nausea, vomiting, diarrhoea</td>
<td>Direct effect of toxins</td>
</tr>
<tr>
<td>5. Tegumentary</td>
<td>Slow healing of wounds</td>
<td>Decreased collagen production</td>
</tr>
<tr>
<td></td>
<td>- Dirty-yellow teguments</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Pruritus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Haemorrhagiparous syndrome</td>
<td></td>
</tr>
<tr>
<td>7. Acid-base balance</td>
<td>Metabolic acidosis</td>
<td>Acid catabolyte accumulation</td>
</tr>
</tbody>
</table>

C. **Complications of CKD**

1. **CARDIOVASCULAR complications**

- Arterial hypertension (AHT)
  – Activation of resistance RAAS → resistant AHT
  – Water and natrium retention → volume AHT
- **Uremic cardiomyopathy** – decreased DC due to decreased contractility
- **Uremic pericarditis** – due to urea crystal precipitate in the pericardium
- **Accelerated ATS** – due to AHT, dyslipidemia and vessel calcification (hypercalcemia) → ischaemic cardiopathy, cardiac arrhythmias, CVA
- **Heart failure** – due to:
  - primary decrease of contractility: ischaemic cardiopathy, uremic cardiopathy
  - secondary decrease of contractility caused by:
    - pressure overcharge: AHT
    - volume overcharge: hydrosaline retention, hyperdynamic condition induced by severe anaemia
    - decreased cardiac filling: uremic pericarditis

2. **PULMONARY complications**
- **Cheynes-Stokes or Kussmaul dyspnoea** – reflex hyperventilation subsequent to the alteration of respiratory centres caused by:
  - metabolic acidosis
  - uremic toxins ("uremic lung")
- **Pulmonary oedema** – due to volume overcharge

3. **DIGESTIVE complications**
- **Anorexia, nausea, vomiting** → induce malnutrition and protein and amino acid deficiency
- **Gastroenteritis and uremic stomatitis**
  - urea is a highly diffusible substance, consequently it is present in the gastric and buccal mucosa where it is decomposed into ammonia by bacterial urease
  - ammonia production:
    - has ulcerative effects → gastroenteritis and uremic stomatitis
    - explains uremic halitosis (uremic factor) of patients with kidney failure
- **Digestive haemorrhages** – from gastrointestinal ulcerations

4. **HAEMATOLOGIC and IMMUNOLOGIC complications**
- **Normocytic normochromic anaemia** – due to:
  - pathological haemolysis caused by uremic toxins (main mechanism)
  - relative erythropoietin deficiency
  - medullary inhibition caused by uremic toxins
  - red blood cell loss subsequent to haemorrhages and gastrointestinal ulcers
- **Suppression of the immune system and increased susceptibility to infections** – due to:
  - decreased chemotacticity and polymorphonuclear phagocytosis capacity
  - decreased humoral and cellular immune response
- **Haemorrhagic syndrome** with increased bleeding risk → prolonged bleeding of cutaneous injuries, purpura, epistaxis, gastrointestinal haemorrhages, haemorrhagic CVA – due to **platelet dysfunction** responsible for:
  - impaired primary haemostasis – decreased platelet aggregation and adhesion (main cause)
  - impaired secondary haemostasis – decreased platelet 3 factor (↓ thrombin activation)

5. **BONE complications** – renal osteodystrophy or osteopathy
- **Spontaneous fractures, bone deformations and pain** – due to:
  - hyperPTH → **fibrocystic osteitis**
  - vitamin D deficiency → **osteomalacia**

6. **NERVOUS complications**
- Caused by the effects of uremic toxins (Table.3)
- Ischaemic or haemorrhagic CVA

7. CUTANEOUS complications (Table.3)

8. SEXUAL complications
   - **Gonadal dysfunction** → decreased level of sexual hormones with infertility and low libido